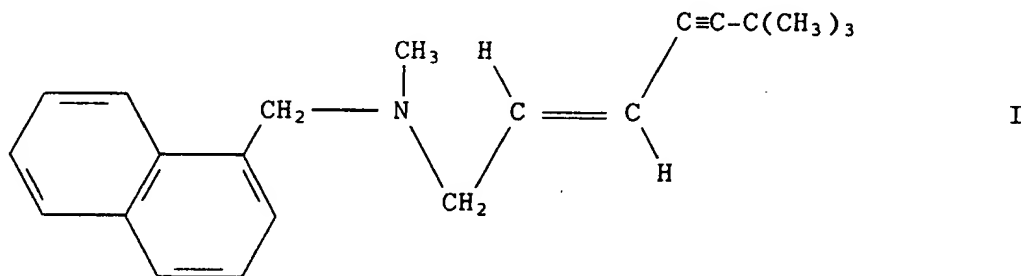


PHARMACEUTICAL COMPOSITION

The present invention relates to topical pharmaceutical compositions, such as solutions, gels, fluid gels, emulsion gels and lotions containing an allylamine compound as the pharmacologically active agent.

The present invention provides a topical pharmaceutical composition, comprising as the active agent a compound of formula I



and a lower alkanol.

Such compositions may be for example non-greasy solutions, emulsion gels or lotions, all being liquid or viscous.

In another aspect the present invention provides a process for the preparation of a topical pharmaceutical composition, comprising working up a compound of formula I above together with a lower alkanol and adding further excipients as appropriate.

Examples of topical solutions contemplated under the present invention are solutions per se or are spray liquids, gels or fluid gels.

Water is preferably present in the compositions according to the invention, e.g. in concentrations by weight from e.g. 50 to 85 %.

The compound of formula I may be e.g. in free base form or in acid addition salt form. An acid addition salt form may be prepared from the free base form in conventional manner and vice-versa. Examples of suitable acid addition salt forms are the hydrochloride, the lactate and the ascorbate.

The compound of formula I is known from e.g. BE-PS-853976 and EP-A-24587. It belongs to the class of allylamine anti-mycotics. It has the generic name terbinafine and is commercially available under the tradename LAMISIL. Whereas terbinafine is highly active upon both topical and oral application, we have found that the only topical formulation for wide-spread use, a cream in which the drug is kept dissolved in the organic phase, only partly fulfills the patients' needs, as it is only a convenient formulation for selected disease states and skin types. A topical formulation in the form of a composition according to the invention is highly desirable as it offers several advantages e.g. in application properties, in comparison to classical formulations such as creams, e.g.

- faster and more complete release of the drug from the vehicle to the skin and therefore higher efficacy;
- absence of greasiness and no residue upon application and therefore increased convenience for application on haired skin;
- improved spreadability on the skin and thus better convenience for application on larger skin parts; and
- cooling effect on the skin and therefore better convenience for application on seborrheic skin.

The preparation of topical compositions offering the improved properties mentioned above, however, is difficult with the compound of formula I due to the low solubility of the drug in aqueous systems, the tendency of the compound when used in acid addition salt form or as an oil based emulsion gel or lotion, to separate from the medium as the free base, as droplets or

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even in crystalline form, as we have found the free base is less soluble in water than the corresponding acid addition salts and due to the tendency of the drug to interact with anionic excipients. Using the acid addition salt form is desirable and also the preferred embodiment of this invention, because the solubility of the drug in aqueous systems may be improved. However, separating of the free base from the equilibrium present in compositions according to present invention presents a serious problem with respect to the reproducibility of the pharmacological effect, and to the shelf life stability of such product.

The above difficulties are exacerbated when attempting to prepare one-phase formulations such as fluid gels and gels containing the compound of formula I in free base or salt form in the same phase in combination with the classical Carbomer thickeners (polyacrylic acid derivatives) which is a typical excipient for gels. We have observed that there is an interaction of the components, resulting in an insoluble complex or in crystallization of the base. There is thus a need for improved topical forms e.g. fluid gels and gels.

As outlined above, this problem can according to one aspect of this invention be circumvented by formulating an emulsion system where the free base is dissolved in the oily phase. However these systems may not be suitable for certain kinds of skin type and disease state as in many situations a formulation substantially free of fatty materials such as fatty acids, fatty acid esters and fatty alcohols such as e.g. polyethylene stearates or palmitates, cetyl stearates or palmitates, stearyl or cetyl alcohols, is preferred. A clear solution is also highly desirable as an improved topical formulation. There is thus also a need for such improved forms which are based on water and do not contain oils or fats and wherein the free base present at equilibrium remains in solution.

According to another aspect of the invention, it has now been found that the separation of the free base in water-based solutions may be avoided e.g. for the topical solutions by the addition of suitable solubilizing

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agents in the formulations, which are non-ionic, e.g. there is no anionic surfactant present. These agents should preferably be surfactants which are water-soluble or water-miscible and compatible with the drug substance and any further excipients present in the formulation, and they should be well tolerated on the skin.

Further, a desirable feature of the contemplated solubilizers is a penetration-enhancing effect for the drug substance without causing any irritation on the skin.

Examples of suitable solubilizing agents for the topical solutions are:

a) Reaction products of a natural or hydrogenated castor oil and ethylene oxide. Such products may be obtained in known manner, e.g. by reaction of a natural or hydrogenated castor oil with ethylene oxide, e.g. in a molar ratio of from about 1:35 to about 1:60, with optional removal of the polyethyleneglycol component from the product, e.g. in accordance with the methods disclosed in DOS 1'182'388 and 1'518'819. Especially suitable are the various tensides available under the tradename Cremophor. Particularly suitable are the products:

- Cremophor RH 40 having a saponification number of about 50-60, an acid number  $< 1$ , an iodine number  $< 1$ , a water content (Fischer)  $< 2\%$ , an  $n_D^{60}$  of about 1.453 - 1.457 and an HLB of about 14-16;
- Cremophor RH 60 having a saponification number of about 40-50, an acid number  $< 1$ , an iodine number  $< 1$ , a water content (Fischer) 4.5-5.5 %, an  $n_D^{25}$  of about 1.453 - 1.457 and an HLB of about 15-17; and
- Cremophor EL having a molecular weight (by steam osmometry) of about 1630, a saponification number of about 65-70, an acid number of about 2, an iodine number of about 28-32 and an  $n_D^{25}$  of about 1.471.

Also suitable for use in this category are the various tensides available under the tradename Nikkol, e.g. Nikkol HCO-60. Nikkol HCO-60 is a reaction product of hydrogenated castor oil and ethylene oxide exhibiting the following characteristics: acid number of 0.3; saponification number of 47.4; hydroxy value of 42.5; pH (5 %) of 4.6; color APHA = 40; M.P. =

36.0°C; freezing point = 32.4°C; H<sub>2</sub>O content (% , KF) = 0.03;

b) polyoxyethylene-sorbitan-fatty acid esters or polysorbates, e.g. of the type known and commercially available under the tradenames Tween (Fiedler 2, p.1300-1304) and Armotan (Fiedler 1, p. 172) including the products

Tween 20 [polyoxyethylene(20)sorbitanmonolaurate];

Tween 40 [polyoxyethylene(20)sorbitanmonopalmitate];

Tween 60 [polyoxyethylene(20)sorbitanmonostearate];

Tween 65 [polyoxyethylene(20)sorbitantristearate];

Tween 80 [polyoxyethylene(20)sorbitanmonooleate];

Tween 85 [polyoxyethylene(20)sorbitantrioleate];

Tween 21 [polyoxyethylene(4)sorbitanmonolaurate];

Tween 61 [polyoxyethylene(4)sorbitanmonostearate]; and

Tween 81 [polyoxyethylene(5)sorbitanmonooleate];

c) polyoxyethylene fatty acid esters, for example polyoxyethylene stearic acid esters of the type known and commercially available under the Tradename Myrj (Fiedler 2, p. 834-835) as well as polyoxyethylene fatty acid esters known and commercially available under the tradename Cetiol HE (Fiedler 1, p. 283-284);

d) polyoxyethylene-polyoxypropylene co-polymers e.g. of the type known and commercially available under the tradenames Pluronic and Emkalyx (Fiedler 2, p. 956-958);

e) polyoxyethylene fatty alcohol ethers, for example polyoxyethylene stearyl ether, oleyl ether, or cetyl ether, e.g. of the type known under the tradename Brij (Fiedler 1, p. 222-224), e.g. Brij 78 and 96, and Cetomacrogol 1000 (Fiedler 1, p. 284).

Preferred solubilizing agents are those under a), b), c) and e), particularly Cetomacrogol 1000<sup>R</sup>, Cremophor RH40<sup>R</sup> and Tween 20<sup>R</sup>. Especially preferred is Cetomacrogol 1000<sup>R</sup>.

The compound of formula I and the solubilizing agent are preferably present in the topical-solution composition in the proportion of from about 1:0.5 to about 1:15, preferably from about 1:1 to about 1:10 on a w/w basis. The compound of formula I preferably makes up from about 0.1 % to about 5 %, preferably from about 0.5 % to about 2 % of the total composition on a weight basis.

In their simplest form the topical solutions of this invention only comprise the drug substance, the solubilizer and the lower alkanolic solvent. The alkanolic solvent is preferably mixed with water when used in a composition according to the invention. Lower alkanolic solvents according to the invention are physiologically acceptable C<sub>1</sub>-C<sub>4</sub> alcohols e.g. isopropanol or preferably ethanol. The concentration by weight of the alkanol in the composition may range e.g. from about 5 % to about 90 %, e.g. from about 5 % to about 35 %. A typical concentration is from about 25 % to about 45 % for a fluid composition, e.g. from 25 to 35%, and for a viscous composition, e.g. a gel from about 5 to about 15 %, e.g. 10 %.

The solutions may be filled into conventional glass bottles with a dropping device or into more elaborate devices, e.g. plastic bottles or plastic bottles with spraying device.

Due to easier application a thickened solution, e.g. a fluid-gel or a transparent gel may be desirable. This can be achieved by adding conventional thickeners to the solutions described above. Suitable components include for example:

- polymethylacrylate resins, e.g. of the type known and commercially available under the tradename Eudispert (Fiedler 1, p. 485-486);
- cellulose derivatives including e.g. ethyl-, propyl-, methyl- and hydroxypropylmethyl-celluloses;
- polyvinyl resins, e.g. including polyvinylalcohols and polyvinylpyrrolidones, as well as other polymeric materials including gelatin, alginates, pectins, gum traganth, gum arabicum and gum xanthane;

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- materials such as silica gel, bentonite, and magnesium-aluminium silicate.

These components when present are suitably present in an amount of up to 20 %, more preferably up to 10 %, based on the total weight of the composition. Most suitably they are present in an amount of from about 0.5 % to about 15 %, e.g. from about 1.0 % to about 3.0 % based on the total weight of the composition.

The topical solution preparations of the invention can be obtained by a process comprising dissolving the compound of formula I in free base form or in acid addition salt form together with the solubilizer in an appropriate vehicle and adding further excipients as appropriate. If a thickened solution or a gel is desired the thickener is added in conventional manner to the system. The process of the invention may be effected in conventional manner.

According to a further aspect of the invention stable emulsion gels and lotions are provided. Where an emulsion gel or a lotion based on a carbomer thickener is required in order to administer the compound of formula I to the skin, the problems associated with the interaction of the free base with the anionic polymer are in principle the same as with the above aqueous solutions. It has now been found that these interactions may be avoided and stable emulsion gels and lotions may be obtained when an oily phase, such as isopropyl myristate, is added to the compound of formula I, preferably in free base form, and the carbomer. This results in stable emulsion gels and lotions which have all the beneficial properties of a gel and avoid the interaction of the drug with the carbomer.

In emulsion gels and lotions according to the invention the compound of formula I and an oil phase are present in the emulsion gels and lotions in the proportion of from about 1 : 5 to about 1 : 40, preferably from about 1 : 7 to about 1 : 20 on a w/w basis. The oil phase is preferably isopropyl myristate. It is preferably present in a concentration by weight of 10 %.

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The compound of formula I preferably makes up from about 0.1 % to about 5 %, preferably from about 0.5 % to about 3 % of the total composition on a weight basis. Preferably the amount of lower alkanol, water and oil phase, if present, is from about 83 to about 96 % by weight of the composition. Conventional further excipients are in particular thickeners such as carbomers (polyacrylic acid derivatives) as known and commercially available under the tradename Carbopol (Fiedler 1, p. 206-207), e.g. Carbopol 934 P or Carbopol 1342. Further excipients are, e.g. emulsifiers such as sorbitan monolaurate (Span 20<sup>R</sup>) and polysorbate 20 (Tween 20<sup>R</sup>); however, it has been observed that with the compound of formula I the carbomers stabilize the emulsion to the extent that only little or no emulgator at all is necessary to achieve stable emulsion gels and lotions, particularly when the carbomer is Carbopol 1342.

The resulting emulsion gels and lotions possess improved cosmetic properties, such as facilitated spreading on the skin and absence of greasing; in view of the reduced amount or absence of conventional emulsifiers, they also possess improved pharmacological properties, in particular better tolerability when applied to infected and often inflamed skin. A further advantage of the present invention is that the appearance and consistency of the final formulation may be freely regulated by varying the proportion of thickening agent (carbomer) in the formulation.

The emulsion gels and lotions of the invention may be obtained by a process comprising dissolving a compound of formula I in free base form or in acid addition salt form and further excipients as appropriate, e.g. in an appropriate oil phase such as isopropyl myristate .

The oil phase may be emulsified with an appropriate water phase and then incorporated into a pre-prepared gel concentrate containing the carbomer and further excipients as appropriate. This mode of manufacturing avoids the interaction between the compound of formula I and the carbomer during the process. Preferably the carbomer is neutralized before being mixed with the oil phase.

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The formulations may contain additional ingredients, e.g.

- complexing agents, e.g. ethylenediamine-tetraacetate (disodium salt);
- flavours;
- colourants.

The compositions according to present invention may also contain conventional additives to adjust the pH-value to an acceptable value for skin treatment. This may be achieved by adding a pharmaceutically acceptable base or acid and adjusting the pH-value or by adding a pharmaceutically acceptable buffer system to the composition. Additionally, the compositions may contain preserving agents and/or antioxidants, e.g. an amount of 0.05 to 1% by weight of the total weight of the composition, e.g. ascorbyl palmitate, sodium pyrosulfite, butyl hydroxy anisole (BHA), butyl hydroxy toluene (BHT), tocopherols, e.g.  $\alpha$ -tocopherol (vitamin E), benzyl alcohol, propyl- or methyl p-hydroxybenzoates.

The compositions of the invention are useful for the same indications as known for other topical compositions, e.g. fungal infections and in the same dosages, e.g. as confirmed by standard clinical trials. Typical effective dosages are achieved when the active agent concentration in the treated skin tissue is between 10 and 10'000 ng per square centimeter. Preferred skin tissue concentrations are between 500 and 2000 ng per square centimeter e.g. 1000 ng per square centimeter e.g. as indicated in standard pharmacological tests. However higher and lower dosages may be effective and may be determined by standard tests. For example the effective concentrations in the treated skin may be achieved when applying e.g. the compound of formula I in form of e.g. a 1 % composition according to the invention over the infected area, e.g. 5 mg active agent per day to a skin area of about 100 square centimeters.

The following Examples illustrate the invention. All temperatures are in degrees Centigrade (r.t. = room temperature):

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Example 1: Topical solution 1 % (spray 1 %)

	Ingredient	Amount (g/100 g)
	Compound I in hydrochloride form	1.0
	Polyethoxy-20-cetylstearyl ether (e.g. Cetomacrogol 1000)	2.0
T0110	Propylene glycol	5.0
	Ethanol 94 % w/w	25.0
	Water demineralized	67.0

Example 2: Gel 1 %

	Ingredient	Amount (g/100 g)
T0111	Compound I in hydrochloride form	1.00
	Disodium edetate dihydrate (e.g. Komplexon III)	0.02
	Polysorbate 20 (e.g. Tween 20)	2.0
	Sodium pyrosulfite	0.02
	Propylene glycol	0.70
	Hydroxypropyl cellulose (e.g. Klucel HF)	1.50
	Ethanol 94 % w/w	35.00
	Water demineralized	59.76

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Example 3: Fluid gel 1 %

Ingredient	Amount (g/100 g)
T,0120	
Compound I in hydrochloride form	1.00
Disodium edetate dihydrate (e.g. Komplexon III)	0.02
Sodium pyrosulfite	0.02
Polyethoxy-40-hydrogenated castor oil (e.g. Cremophor RH40)	1.00
Hydroxypropyl cellulose (e.g. Klucel GF)	2.00
Ethanol 94 % w/w	35.00
Water demineralized	60.96

Example 4: Emulsion gel 1 %

Ingredient	Amount (g/100 g)
T,0121	
A) Compound I in free base form	1.00
C) Butyl hydroxy toluene	0.02
I) Sodium hydroxide pellets	0.10
D) Benzyl alcohol	1.00
G) Carbomer 934 (e.g. Carbopol 934 P)	1.00
E) Sorbitan monolaurate (e.g. Span 20)	1.00
F) Polysorbate 20 (e.g. Tween 20)	5.00
H) Ethanol 94 % w/w	10.00
B) Isopropyl myristate	10.00
Water demineralized	70.88

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A pharmaceutically acceptable emulsion gel is obtained from the above ingredients, when the preparation process is carried out in the following steps:

- I. A, B, C, D, E and F are mixed together with slight warming until all solid particles are dissolved;
- II. in an appropriate vessel or processor containing a stirrer and a homogenizer about half of the water is heated to 60-70°;
- III. I is slowly added to II while stirring and homogenizing until a homogenous emulsion with appropriate droplet size is obtained. The concentrated emulsion is then cooled to r.t.;
- IV. in a separate vessel a basic carbomer gel is prepared by dispersing carbomer in H and the second half of the water and neutralizing with I;
- V. the basic emulsion III is added to the basic gel and the whole is stirred at r.t. until a homogeneous emulsion gel is obtained.

Example 5: Emulsion gel 1 %

T.0130

	Ingredient	Amount (g/100 g)
A)	Compound I in free base form	1.00
C)	Butyl hydroxy toluene	0.02
I)	Sodium hydroxide pellets	0.10
D)	Benzyl alcohol	0.50
G)	Carbomer 934 (e.g. Carbopol 934 P)	1.00
E)	Sorbitan monolaurate (e.g. Span 20)	1.00
F)	Polysorbate 20 (e.g. Tween 20)	5.00

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H)	Ethanol 94 % w/w	10.00
B)	Isopropyl myristate	10.00
	Water demineralized	71.33

A pharmaceutically acceptable emulsion gel is obtained from the above ingredients, when the preparation process is carried out in the following steps:

- I. A, B, C, D, E and F are mixed together with slight warming until all solid particles are dissolved;
- II. in an appropriate vessel or processor containing a stirrer and a homogenizer about half of the water is heated to 60-70°;
- III. I is slowly added to II while stirring and homogenizing until a homogenous emulsion with appropriate droplet size is obtained. The concentrated emulsion is then cooled to r.t.;
- IV. in a separate vessel a basic carbomer gel is prepared by dispersing carbomer in H and the second half of the water and neutralizing with I;
- V. the basic emulsion III is added to the basic gel and the whole is stirred at r.t. until a homogeneous emulsion gel is obtained.

Example 6: Lotion 1 %

T0140

	Ingredient	Amount (g/100 g)
A)	Compound I in free base form	1.00
C)	Propyl p-hydroxybenzoate	0.03
D)	Methyl p-hydroxybenzoate	0.10

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G)	Ammonia solution 25 % w/w	0.36
F)	Carbomer (e.g. Carbopol 1342)	0.60
B)	Isopropyl myristate	5.00
H)	Ethanol 94 % w/w	10.00
E)	Water demineralized	82.91

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A pharmaceutically acceptable lotion is obtained from the above ingredients, when the preparation process is carried out in the following steps:

- I. A is dissolved in B at r.t.;
- II. in an appropriate processor containing a stirrer and an efficient homogenizer C and D are dissolved in E while heating up to 90°. The solution is then cooled to about 30 to 40°;
- III. F is dispersed in II. The homogenous dispersion is then neutralized with G, resulting in an opalescent thickened solution;
- IV. the organic solution I is then emulsified into the thickened solution III by stirring and homogenizing until a lotion with appropriate droplet size (2 to 20  $\mu$ m) is obtained;
- V. finally H is added to IV and the whole is stirred until the final product is obtained.